

Applicant : Masayuki Tsuchiya et al.
Serial No. : 09/830,144
Filed : April 20, 2001
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Attorney's Docket No.: 14875-076001 / C1-005PCT-US

REMARKS

It is respectfully requested that this application be reconsidered in view of the above amendments and the following remarks and that all of the claims remaining be allowed.

Amendments in the Specification

The section "Brief Description of the Drawings" (page 48, line 26 to page 49, line 12) has been moved to page 2, line 21, before "Disclosure of the Invention". No new matter is introduced.

Claim Amendments

Claims 2-67 have been canceled without prejudice or disclaimer.

New claims 68-87 have been added. Support for claim 68 can be found, for example, at page 40, lines 6-10 and in canceled claims 67 and 51. Claims 69-87 correspond to claims 2-9, 42, 46-48, 52, 53, 27, and 54-57, respectively, except that the new claims depend from claim 68.

No new matter has been added by these amendments. The Examiner is hereby requested to enter these amendments.

Applicants submit that all claim amendments presented herein or previously are made solely in the interest of expediting allowance of the claims and should not be interpreted as acquiescence to any rejections or ground of unpatentability. Applicants reserve the right to file at least one continuing application to pursue any subject matter that is canceled or removed from prosecution due to the amendments.

Objection to the Specification

The specification stands objected to because the "Brief Description of the Drawings" section is allegedly not in the preferred location in the specification. This section has been moved before "Disclosure of the Invention", and after "Background Art". Therefore, withdrawal of this objection is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph, Enablement (Pages 3-11 of the Office Action)

A. The rejection of claims 2-11, 27, 41-47, 49, 50 and 54-60 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement with respect to the scope of TAK1 and TAB1, is now moot since all of these claims have been canceled.

Claims 68-87 are pending. Applicants submit that this rejection is not applicable to any of the currently pending claims for the reasons set forth below. Claim 68 is directed to a method for screening compounds inhibiting production of an inflammatory cytokine, comprising:

- (a) providing a sample comprising a TAK1 and a TAB1;
- (b) contacting a test compound with the TAK1 and the TAB1;
- (c) detecting binding between the TAK1 and the TAB1; and
- (d) selecting a compound that inhibits the binding;

wherein the TAK1 of (a) is selected from the group consisting of

- (i) a protein comprising amino acids 76 to 303 of SEQ ID NO:2; and
- (ii) a protein that binds to amino acids 437 to 504 of SEQ ID NO:4 and comprises an amino acid sequence encoded by a DNA sequence that hybridizes with the complement of nucleotides 408 to 1091 of SEQ ID NO:1 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide;

and wherein the TAB1 of (a) is selected from the group consisting of

- (iii) a protein comprising amino acids 437 to 504 of SEQ ID NO:4; and
- (iv) a protein that binds to amino acids 76 to 303 of SEQ ID NO:2 and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

With respect to TAK1 and TAB1, the Office Action states that the specification is enabling for

a method of screening for compounds that inhibit the binding of the TAK1 set forth by residues 76-303 of SEQ ID NO:2, or variants thereof comprising 1-20 or 1-10 altered amino acid residues or variants thereof that hybridize under high stringency conditions with residues 408-1091 or SEQ ID NO:1 with a TAB1 set for the by residues 437-504 of SEQ ID NO:4, or variants thereof that hybridize

under high stringency conditions with residues 1338-1541 of SEQ ID NO:3 (last paragraph on page 3 of the Office Action).

The Office Action also indicates that the specification is enabling wherein TAB1 is set forth by SEQ ID NO:4; or is a fragment thereof comprising residues 437-504 of SEQ ID NO:4; or is a variant comprising residues 437-504, with one or two residues changed; or is any variant wherein the polynucleotide encoding the variant hybridizes to SEQ ID NO:3 under high stringency conditions (last 5 lines of the middle paragraph on page 4 of the Office Action).

Claim 68 is limited to the TAK1 and TAB1 that the Examiner has agreed are enabled. All other currently pending claims depend from claim 68, directly or indirectly, and hence encompass only the enabled TAK1 and TAB1. Accordingly, this rejection is not applicable to the currently pending claims.

B. Claims 2-11, 27 and 41-60 under 35 U.S.C. §112, first paragraph, stand rejected for allegedly not being enabled. Specifically, the Office Action states that the specification is enabling for testing the effect of inhibitors of TAK1/TAB1 binding on TGF- β -induced expression of inflammatory cytokines, but it allegedly does not reasonably provide enablement for testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to any activator. This rejection is now moot in view of cancellation of the rejected claims. Furthermore, since the currently pending claims do not recite such testing, they are not subject to this rejection.

Rejections Under 35 U.S.C. §112, First Paragraph, Written Description (Pages 11-15 of the Office Action)

A. The rejection of claims 2-11, 27, 41-47, 49, 50 and 54-60 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed, is now moot because all the rejected claims have been canceled.

Furthermore, it appears that the rejection would not apply to new claims 68-87. In this rejection, the Office Action alleges that the claimed genus of TAB1 is not sufficiently described. The Office Action, however, does not reject claim 48 or 51-53 on this ground. Claims 48 and 51-53 are reproduced below:

48. The method of claim 41, wherein the TAB1 of (a) comprises the amino acids 437 to 504 of SEQ ID NO:4.

51. The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises amino acids 437-504 of SEQ ID NO:4, with one or two amino acids substituted, deleted, and/or added.

52. The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulfate, and 50% formamide.

53. The method of claim 41, wherein the TAB1 of (a) is a protein that binds to the TAK1 of (a) and comprises an amino acid sequence encoded by a DNA that hybridizes with the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 60°C, 0.1 x SSC, and 0.1% sodium dodecyl sulfate.

The TAB1 recited in new claims 68-87 encompasses only the TAB1 recited in the above claims, which apparently complied with the written description requirement. Therefore, this rejection is not applicable to the currently pending claims.

B. The rejection of claims 2-11, 27, and 41-60 under 35 U.S.C. §112, first paragraph, allegedly for insufficient written description, is now moot because these claims have been canceled.

This rejection is not applicable to the currently pending claims. The Office Action alleges that the rejected claims are directed to methods for testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to a genus of activators, while only one representative species of the genus is described. Since the currently pending claims do not involve such testing, there is no need to discuss the propriety of this rejection.

Rejection Under 35 U.S.C. §103 (Pages 15-20 of the Office Action)

A. The rejection of claims 2-11, 27, 41, 42 and 54-59 under 35 U.S.C. §103(a) over Shibuya et al. (Science 272(5265):1179-82, 1996; herein after "Shibuya") in view of McCartney-Francis et al. (Int. Rev. Immunol. 16(5-6):553-80, 1998; hereinafter "McCartney-Francis"), Letterio et al. (Annu. Rev. Immunol. 16:137-61, 1998; hereinafter "Letterio") and Maeda et al. (J. Immunol. 155(10):4926-32, 1995; hereinafter "Maeda") is now moot since all of these claims have been canceled. To the extent that this rejection may be applied to new claims 68-87, Applicants respectfully traverse.

To properly issue a rejection under 35 U.S.C. §103, the USPTO bears the initial burden to establish a *prima facie* case of obviousness by meeting three criteria. One of the criteria is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings to arrive at the claimed invention. *In re Vaeck*, 20 USPQ 2d 1438 (Fed. Cir. 1991). In addition, there must be a reasonable expectation of success. *Id.*

The present rejection does not meet these criteria. As discussed above, claim 68 is directed to a method for screening compounds inhibiting production of an inflammatory cytokine, comprising:

- (a) providing a sample comprising a TAK1 and a TAB1;
- (b) contacting a test compound with the TAK1 and the TAB1;
- (c) detecting binding between the TAK1 and the TAB1; and
- (d) selecting a compound that inhibits the binding;

wherein the TAK1 and TAB1 are as specified in the claim. All other currently pending claims ultimately depend from claim 68.

Shibuya teaches that TAK1 binds to TAB1, and that TAB1 may function as an activator of TAK1 in TGF- β signal transduction. As the Office Action correctly points out, Shibuya does not teach or suggest testing a compound that inhibits TAK1/TAB1 binding for inhibiting expression

of inflammatory cytokines. In fact, Shibuya does not teach or suggest that TAK1 or TAB1 has any role in inflammation.

McCartney-Francis and Letterio provide a review of TGF- β structure, function and signal transduction pathways. It is evident from each of these articles that TGF- β is a pleiotropic factor and acts on diverse tissue and cell types, including epithelial, endothelial, and hematopoietic cells. In the immune system, TGF- β has multiple roles, such as in the generation of dendritic cells, B cell activation and differentiation, monocyte/macrophage function, and inflammation. Furthermore, the references teach that even for a given target tissue or biological phenomenon, TGF- β may have opposing effects. As stated in McCartney-Francis (second paragraph on page 565):

The bifunctional nature of TGF- β is probably most notable in the regulation of immune response. As a naturally occurring immunoregulatory molecule, TGF- β can promote the inflammatory process... On the other hand, TGF- β is a powerful immunosuppressant and is instrumental in the resolution phase of the inflammatory response and wound healing. The balance between these two opposing activities is crucial to maintaining immunological homeostasis in the host...

Thus, TGF- β has both pro-inflammatory and anti-inflammatory activities, in addition to many other functions unrelated to inflammation. It was also known that there are multiple receptors and signal transduction mediators for TGF- β (see, for example, pages 556-559 of McCartney-Francis). Nothing in these references teaches the function of TAK1-TAB1. As such, there is no motivation or suggestion for a skilled artisan to combine Shibuya, McCartney-Francis and/or Letterio and come to the conclusion that TAK1-TAB1 mediates the pro-inflammatory function of TGF- β , rather than another TGF- β activity. The combined teaching also provides no reasonable expectation of success for the claimed invention, as TAK1-TAB1 may be responsible for any of the numerous other TGF- β functions instead of inflammation.

Maeda teaches that TGF- β enhances the ability of macrophages to produce IL-10. However, Maeda does not teach or suggest that this effect of TGF- β is mediated by TAK1-TAB1.

Therefore, like McCartney-Francis and Letterio, Maeda does not offer the required motivation/suggestion or expectation of success for the claimed invention.

The Office Action alleges that since it is known that TGF- β stimulates the expression of IL-1, IL-6, and TNF (taught by McCartney-Francis and Letterio) as well as IL-10 (taught by Maeda), “it would be obvious to a person of ordinary skill in the art to test any compound that inhibits TAK1/TAB1 binding for inhibiting TGF- β -induced expression of IL-1, IL-6, IL-10 and TNF” (page 16, lines 9-14 of the Office Action). This proposition is flawed for the reasons articulated above. McCartney-Francis and Letterio teach numerous functions of TGF- β in addition to stimulating the expression of IL-1, IL-6 or TNF; Maeda is focused on IL-10, but it is known in the art that TGF- β exerts a number of functions by multiple signal transduction pathways. As the Court for Customs and Patent Appeals stated in *In re Ruschig*, 154 USPQ 118, 122 (CCPA 1967):

It is an old custom in the woods to mark trails by making blaze marks on the trees. It is no help in finding a trail...to be confronted simply by a large number of unmarked trees. Appellants are pointing to trees. We are looking for blaze marks which single out particular trees. We see none.

The Office Action points to a large number of trees without blaze marks, but offers no help in finding a trail to the claimed invention. Therefore, a *prima facie* case of obviousness cannot be established.

B. The rejection of claims 43-53 under 35 U.S.C. §103(a) over Shibuya in view of McCartney-Francis, Letterio, Maeda, and further in view of Wells et al. (U.S. Patent No. 5,580,723, hereinafter “Wells”) is moot in view of cancellation of claims 43-53. For the same reasons set forth above, currently pending claims 68-87 are not subject to this rejection.

Briefly, the Office Action argues as above that Shibuya, McCartney-Francis, Letterio, and Maeda allegedly provide the motivation/suggestion and expectation of success with respect to the use of TAK1-TAB1 in inflammation. The Office Action further states that it is common in the art to make and use peptide variants in binding reactions, as taught by Wells, and concludes that a person of ordinary skill would have been motivated to employ TAK1 or TAB1 variants in

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the claimed invention. However, as discussed above, Shibuya, McCartney-Francis, Letterio, and Maeda do not provide the required motivation/suggestion, or "blaze marks", that would lead to the claimed invention. The combined reference teaching also does not provide a reasonable expectation of success. Wells teaches methods of systemically analyzing the structure and function of peptides. Wells does not disclose any information about TAK1, TAB1, or inflammation, and does not cure the deficiency of the other cited references. Therefore, no *prima facie* case of obviousness has been established.

Conclusions

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of all the pending claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at (617) 542-5070 or the undersigned's associate, Ping Hwung, at (650) 839-5044.

Enclosed is a \$790.00 check for the RCE fee required under 37 CFR 1.17(e) and a \$430.00 check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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